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Reelin protein marks cocaine-sensitive *Drd1+* medium spiny neurons and modulates the transcriptional and physiological response to dopamine

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Reelin, a large, secreted glycoprotein encoded by the gene *Reln*, is expressed highly in the adult striatum, hippocampus, and cerebellum. *Reln* expression plays a critical role in brain development and experience-dependent plasticity. While the role of reelin protein in neurodevelopment has been extensively studied, reelin's cellular and molecular role in the adult brain remains to be characterized, despite genetic links to neuropsychiatric disorders, such as psychostimulant abuse. To assess *Reln* mRNA distribution within specific cell types of the rat nucleus accumbens (NAc), we queried a recently described transcriptional atlas generated from single-nucleus RNA-seq of rat NAc tissue collected following acute cocaine exposure. This dataset demonstrated that *Reln* mRNA marks a population of cocaine-responsive *Drd-1+* medium spiny neurons (MSNs). These results were mirrored in postmortem human brain tissue, where multiplexed fluorescent in-situ hybridization showed enrichment of *RELN* mRNA in NAc *Drd1+* MSNs. We next designed a CRISPR sgRNA targeting the *Reln* promoter, allowing us to bidirectionally manipulate *Reln* mRNA and protein levels with CRISPR activation or CRISPR interference. Notably, CRISPR activation of *Reln* in rat primary striatal neuron cultures enhanced stimulus-dependent transcription of immediate early genes (IEGs) following dopamine stimulation. Likewise, knockdown of *Reln* blunted the dopamine-induced increases in MSN firing rate, without altering baseline electrophysiological properties. Additionally, purified Reelin robustly induces expression of IEGs, an effect increased with dopamine treatment. Together, these results suggest Reelin may contribute to dopamine-dependent transcriptional and physiological changes caused by cocaine. Ongoing studies are assessing the effects of CRISPR-mediated *Reln* manipulations on cocaine-induced behavioral responses.